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Amygdala alterations during an emotional conflict task in women recovered from anorexia nervosa

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ABSTRACT

The pathophysiology of anorexia nervosa (AN) is not completely understood, but research suggests that alterations in brain circuits related to cognitive control and emotion are central. The aim of this study was to explore neural responses to an emotional conflict task in women recovered from AN. Functional magnetic resonance imaging was used to measure neural responses to an emotional conflict task in 22 women recovered from AN and 21 age-matched healthy controls. The task involved categorizing affective faces while ignoring affective words. Face and word stimuli were either congruent (non-conflict) or incongruent (conflict). Brain responses to emotional conflict did not differ between groups. However, in response to emotional non-conflict, women recovered from AN relative to healthy controls showed significantly less activation in the bilateral amygdala. Specifically, while emotional non-conflict evoked significant activations of the amygdala in healthy controls, recovered AN women did not show such activations. Similar significant group differences were also observed in the hippocampus and basal ganglia. These results suggest that women recovered from AN are characterized by alterations within emotion-related brain circuits. Recovered women's absence of amygdala and hippocampus activation during non-conflict trials possibly reflects an impaired ability to process emotional significant stimuli.

1. Introduction

Anorexia nervosa (AN) is a potentially fatal mental disorder that predominantly affects adolescent females (American Psychiatric Association, 2013). It is characterized by a relentless pursuit of thinness, severe food restriction, and extremely low body weight. Patients with AN have an intense fear of weight gain and a distorted view of their own body; viewing themselves as fat despite being emaciated. Furthermore, patients are characterized by personality traits such as perfectionism, neuroticism and obsessive-compulsiveness (Cassin and von Ranson, 2005), and they display high anxiety (Holtkamp et al., 2005; Pollice et al., 1997).

The pathophysiology of AN is not completely understood, but available evidence suggests that alterations in brain circuits related to cognitive control and emotion are central (Kaye et al., 2013). Cognitive control refers to higher order cognitive functions such as working memory, monitoring, mental flexibility, planning and inhibition, and enables regulation of behavior, cognition and emotions in accordance with current goals (Chan et al., 2008; Miller and Cohen, 2001). The neurocircuitry underlying these functions mainly resides in prefrontal and anterior cingulate cortices, which monitor and exert top-down control over other brain circuits (Miller and Cohen, 2001). For instance, inadequate top-down control from the prefrontal cortex over subcortical (e.g., limbic) structures is associated with poor regulation of behavior and emotion (Heatherton and Wagner, 2011). In a similar vein, some have raised the possibility that an imbalance between cognitive control and emotion circuits underlies the pathophysiology of AN (Holliday et al., 2005; Kaye et al., 2013; Marsh et al., 2009), which could be associated with patients' extraordinary ability to inhibit incentive motivational drives (i.e. hunger), and the difficulties with emotional regulation that they display (Kaye et al., 2013).

Studies challenging cognitive control have reported that AN is associated with alterations in prefrontal and anterior cingulate cortices (Ehrlich et al., 2015; Lao-Kaim et al., 2015; Oberndorfer et al., 2011; Sato et al., 2013; Wierenga et al., 2014, 2015; Zastrow et al., 2009). For example, women recovered from AN show increased activation in the lateral prefrontal cortex during monetary decision tasks (Ehrlich et al., 2015; Wierenga et al., 2015), possibly

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reflecting elevated cognitive control processes. Studies investigating cognitive-behavioral flexibility in ill AN patients have also reported alterations in the prefrontal cortices, although results are mixed, with some showing decreased activation in patients (Sato et al., 2013; Zastrow et al., 2009), and others showing both decreased and increased activations (Lao-Kaim et al., 2015). It has also been demonstrated that while patients with AN have similar neural activation to healthy controls during low-demanding inhibitory trials, they exhibit decreased activation in the prefrontal and anterior cingulate cortex during high-demanding inhibitory trials (Wierenga et al., 2014). A similar demand-specific alteration of prefrontal cortices has been shown in recovered AN patients (Oberndorfer et al., 2011). These studies suggest AN individuals require less inhibitory resources to maintain performance as inhibitory demand increases. Interestingly, studies have also reported altered functional connectivity within cognitive control circuits during rest in AN individuals, but results are mixed: some report increased functional connectivity (Boehm et al., 2014; Cowdrey et al., 2012), while others report decreased connectivity (Gaudio et al., 2015; Kullmann et al., 2014b). These inconsistencies may be due to small sample sizes, or differences in sample characteristics. In sum, there are clear indications that both ill and recovered AN individuals are characterized by aberrations in cognitive control circuits.

Ample evidence suggests that AN is also associated with functional alterations within emotion circuits related to the perception and processing of emotionally salient stimuli. The majority of this research has been performed using symptom-provocation paradigms, where stimuli are AN-specific (i.e., images of food and bodies). When exposed to such stimuli, patients with AN relative to healthy controls exhibit greater activation in widespread cortical and subcortical brain circuits (Zhu et al., 2012), including anterior cingulate (Ellison et al., 1998; Uher et al., 2004), prefrontal (Ellison et al., 1998; Miyake et al., 2010; Uher et al., 2004), and amygdala cortices (Ellison et al., 1998; Joos et al., 2011; Miyake et al., 2010; Seeger et al., 2002; Vocks et al., 2010, 2011). These hyperactivations have been interpreted as representing heightened negative emotional arousal. The alterations in prefrontal and anterior cingulate cortices may indicate that compensatory control mechanisms are mobilized, for example to regulate amygdala activation. Consistent with this notion, Pruis et al., (2012) showed that negative emotional distractors (images of bodies) during a working memory task were associated with greater amygdala activation and reduced medial prefrontal cortex activation in recovered AN patients compared with healthy controls. This might point to a failure of prefrontal circuits to adequately inhibit amygdala activation. As most studies of emotion processing in AN have employed disorder-specific stimuli, it remains unclear to what extent the reported alterations are restricted to the processing of such stimuli, or are indicative of a general deficit in emotion processing.

Collectively, these studies indicate that the pathophysiology of AN is associated with alterations within both emotion and cognitive control circuits. However, few studies have attempted to characterize these alterations during tasks that require cognitive control in the presence of emotional stimuli. The aim of the present study was to explore this in women recovered from AN. To achieve this, an emotional conflict task was presented during functional magnetic resonance imaging (MRI). Performance on this task relies on cognitive control processes such as conflict detection and inhibition (Etkin et al., 2006). To our knowledge, this is the first study of AN to challenge cognitive control in the context of emotional stimuli unrelated to AN symptomatology.

2. Methods

2.1. Participants

We recruited 22 adult women recovered from AN and 21 age-matched healthy control women, all right-handed. Current and lifetime DSM-IV diagnoses (American Psychiatric Association, 2000) were determined with the Structured Clinical Interview for DSM-IV Axis I Disorders version I/P (First et al., 2002), which was administered to all participants no more than 1 week before the MRI session. During this interview, the status of AN recovery was evaluated (see below), and other clinical characteristics were obtained.

Women in the recovered AN group were included if they had a lifetime history of AN to DSM-IV criteria (American Psychiatric Association, 2000), which included (a) a weight below 85% of that expected based on height and age, (b) intense fear of weight gain or becoming fat, and (c) body image disturbances, or undue influence of body shape or weight on self-evaluation, or denial of the seriousness of their low body weight. Similar to other studies (Pruis et al., 2012), we excluded the amenorrhea criterion which was also removed in the DSM-5 (American Psychiatric Association, 2013). We also subtyped participants into restricting versus binge-eating/purging type, based on the presence of binging or purging behavior during the AN period (American Psychiatric Association, 2013). Only women recovered from AN were included in this study. Recovery was operationally defined as having maintained a body mass index above 18.0 for the past 12 months, and abstinence from binging and purging behavior, excessive or compulsive exercising behavior, and no severely restricted food intake for the past 12 months. Exclusion criteria for these women included the following: lifetime history of a psychotic disorder, substance abuse or dependence, or the presence of any Axis I disorder the past 12 months.

Exclusion criteria for women in the control group included the following: lifetime history of any Axis I disorder, current use of psychoactive medications, and a first-degree relative with a history of an eating disorder. Furthermore, we excluded control women who reported binging and purging behavior, excessive and compulsive exercising, severely restricted food intake, or had a body mass index below 18.0 for the past 12 months. Women in both groups were excluded if they reported any major medical illnesses, history of severe head trauma, or any contraindications to magnetic resonance imaging (MRI).

Three of the recovered AN women were using psychoactive medications (one for insomnia, and two for depressive symptoms), but results did not change when these women were excluded, so they were included in the final analyses. This study was approved by the Regional Ethics Committee in Norway. After complete description of the study, written informed consent was obtained from all participants.

2.2. Behavioral measures

Immediately before the MRI session, all participants completed the following self-report questionnaires: Spielberger State-Trait Anxiety Inventory (STAI; Spielberger et al., 1970), Difficulties in Emotion Regulation Scale (DERS; Gratz and Roemer, 2004), Beck Depression Inventory (BDI; Beck et al., 1961), and Eating Disorder Examination-Questionnaire (EDE-Q; Fairburn and Beglin, 2008). Following the MRI session, participants were weighed in order to calculate their body mass index.

2.3. Emotional conflict task

The emotional conflict task was similar to that used in previous